

Challenges and discoveries in the total synthesis of complex

5 polyketide natural products[‡]

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10 [‡] *Dedicated to Professor K. C. Nicolaou, a master of the art and craft of total synthesis*

Abstract

Structurally complex polyketide natural products, isolated from a variety of marine and terrestrial sources, continue to provide a valuable source of rewarding targets for the synthetic
15 chemist to tackle. In this account, we provide an overview of the total synthesis of several structurally fascinating polyketides with promising anticancer activity completed in our group based on our versatile asymmetric aldol methodology – spirastrellolide A methyl ester, leiodermatolide, rhizopodin and chivosazole F – and highlight the unanticipated challenges and discoveries encountered.

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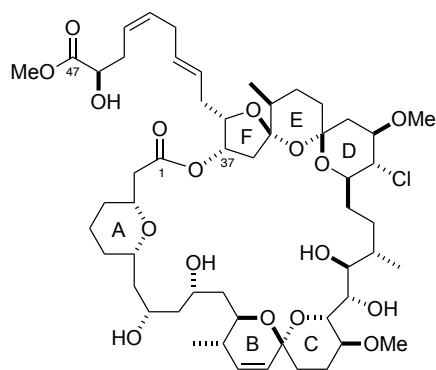
Introduction

Through aeons of evolution, nature has gifted us with a seemingly limitless source of important secondary metabolites. Such compounds are often astoundingly intricate in terms of their molecular architecture, with stereochemically elaborate scaffolds that dwarf structures

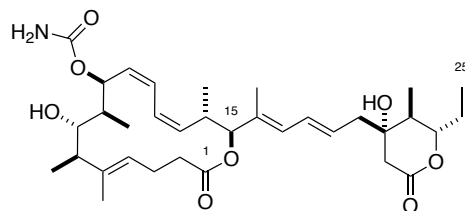
25 conceived by mankind. Unsurprisingly, such extraordinary structures demand effective methodologies and strategies, along with hard work and perseverance, to ensure a successful outcome from a suitably focused synthetic campaign. Furthermore, the vanishingly low isolation yields of such natural products can preclude their full stereochemical assignment, rendering total synthesis a valuable tool for structural elucidation.¹⁻⁵

30 Amongst the vast chemical space carved out by nature are the polyketides, typified by their dazzling array of functionality and stereochemistry, providing a testing intellectual challenge for the synthetic chemist. Enticed by these intriguing structures, which generally have impressive biological activities,⁶ our group has had a longstanding interest in the development of novel synthetic methods and strategies that are both robust and, where required, flexible. In
35 this context, the efficiency of our suite of versatile boron-mediated aldol reactions has proved invaluable for the controlled installation of the highly oxygenated frameworks of these captivating natural products.⁷⁻⁹

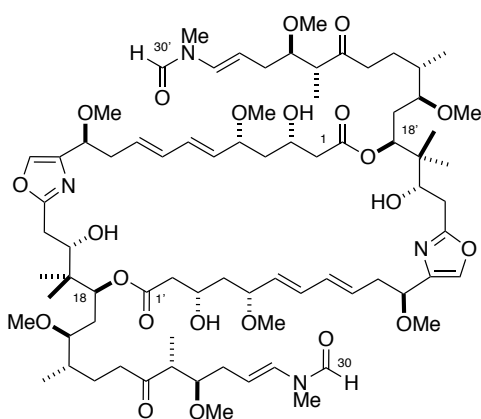
In this account, we provide an overview of recent research endeavors that have culminated in the total synthesis of several challenging polyketide natural products with promising
40 anticancer activity in our group: spirastrellolide A methyl ester (**1**), leiodermatolide (**2**), rhizopodin (**3**), and chivosazole F (**4**) (**Figure 1**). In particular, we highlight the unexpected obstacles encountered and subsequent discoveries that resulted in the successful total syntheses of these highly challenging targets.



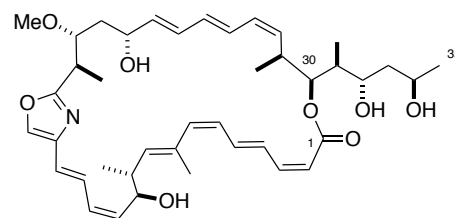
Spirastrellolide A methyl ester (1)



Leiodermatolide (2)



Rhizopodin (3)



Chivosazole F (4)

Figure 1. Structures of spirastrellolide A methyl ester (1), leiodermatolide (2), rhizopodin (3) and chivosazole F (4)

Spirastrellolide A methyl ester

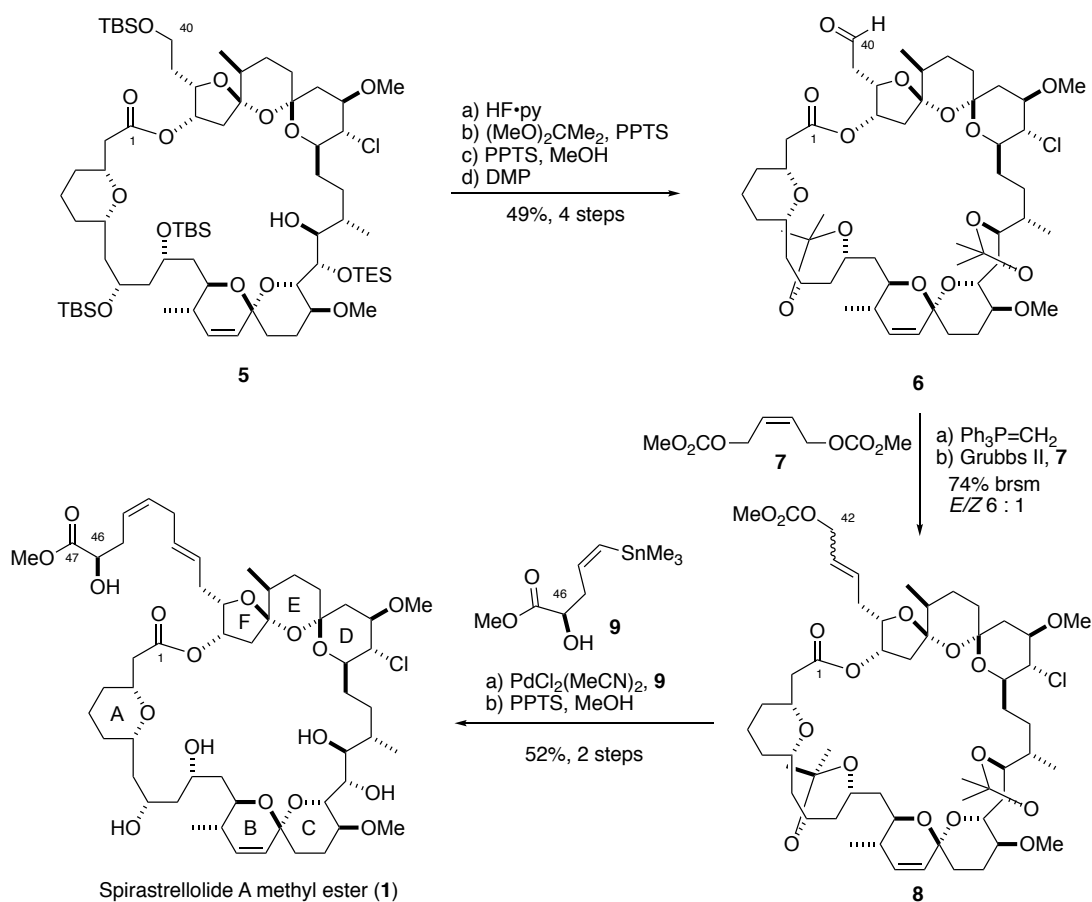
The spirastrellolides constitute an extraordinary family of spiroacetal macrolides first isolated by Andersen and co-workers in 2003 from extracts of the Caribbean sponge *Spirastrella coccinea*.¹⁰ The most abundant congener, spirastrellolide A (1) (isolated as the corresponding methyl ester) exhibits striking structural complexity, containing 20 stereocentres, a 38-membered macrolactone and a nine-carbon side chain featuring a (Z,E)-1,4-diene.^{11–15} The macrocycle itself contains a tetrahydropyran (A ring), a bicyclic 6,6-spiroacetal (BC rings) and a tricyclic 5,6,6-spiroacetal (DEF rings) featuring a chlorine atom

at C28. Additionally, spirastrellolide A was found to exhibit potent antimitotic properties *via* selective protein phosphatase 2A inhibition ($IC_{50} = 1 \text{ nM}$).^{10,12} Beyond the obvious potential as a novel anticancer lead, such phosphatase inhibitors have also shown therapeutic promise in tackling obesity, autoimmune conditions and neurodegenerative disorders.¹⁶ The combination of the synthetic challenge posed by their architectural complexity and promising biological activity has rendered the spirastrellolides the focus of intense research efforts from numerous groups.¹⁵ Despite this, only five completed syntheses have been reported to date,<sup>17–
20</sup> two of which are from our group.^{21–24}

Our efforts towards spirastrellolide A methyl ester began soon after disclosure of the originally proposed structure and our synthetic approach evolved concurrently with structural determination studies on this moving target.²⁵ A flexible endgame was a strict requirement as a consequence of the ambiguity surrounding the C46 hydroxyl stereocentre. Specifically, our initial strategy in face of these imposed requirements involved a modular approach to macrocycle formation, resulting in the successful assembly of the complete ABCDEF ring system, followed by late-stage side chain attachment to facilitate preparation of both possible C46 diastereomers.²⁶

With advanced intermediate **5** (**Scheme 1**) in hand after a sustained campaign of dedicated efforts,^{22,26} synthesis completion appeared tantalisingly close. Unfortunately, selective removal of the C40 silyl protecting group to enable side chain incorporation proved to be a major obstacle. In the end, a global deprotection, followed by protecting group adjustment, was required. Oxidation to the corresponding aldehyde **6** then proceeded smoothly and set the scene for homologation. At this point, a variety of organometallic addition reactions were trialled unsuccessfully. We surmised that these failures were likely to be a reflection of the steric constraints imposed on the C40 aldehyde by the proximal cage-like macrocycle. After exhaustive experimentation, it was found that a simple Wittig olefination

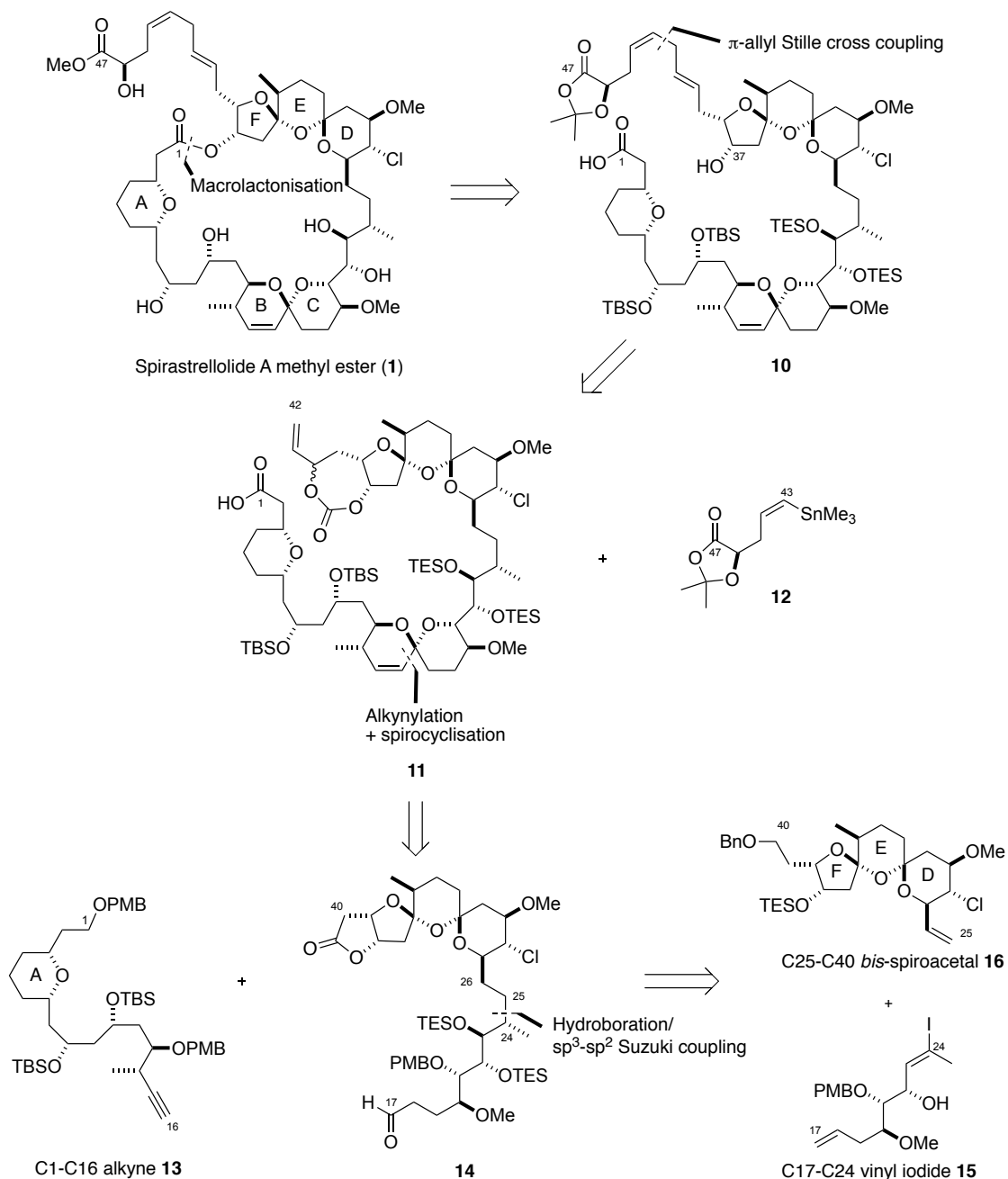
reaction could be used to access a terminal alkene, thereby allowing side chain incorporation *via* olefin cross-metathesis.^{27,28} After considerable experimentation, the cross-metathesis with dicarbonate **7** required relatively forcing conditions (refluxing in benzene), due to the steric constraints imposed by the macrocycle. The resulting allylic carbonate **8** then allowed a π -allyl Stille cross-coupling with stannane **9** to afford the *bis*-acetonide protected natural product, which underwent a global deprotection to afford the first total synthesis of spirastrellolide A methyl ester (**1**).²² Notably, the 46-*epi* diastereomer of **1** showed distinctly different NMR spectra due to the influence of the proximate macrocycle.



Scheme 1. Endgame sequence for the first-generation synthesis of spirastrellolide A methyl ester (**1**)

Having successfully completed the target molecule, and thereby validating the configurational assignment, we next sought to improve our synthesis, paying specific attention to avoiding unnecessary redox steps and protecting group manipulations. In particular, the

need for a divergent side-chain installation strategy was now deemed unnecessary with the stereochemistry of the natural product now unambiguously assigned. Additionally, we sought to capitalise on the availability of key fragments from our first-generation approach, giving rise to the revised retrosynthetic analysis in **Scheme 2**. Notably, we looked to establish the C1-C47 carbon backbone in **10** (from allylic carbonate **11** and stannane **12**) in its entirety prior to macrolactonisation, thereby simplifying incorporation of the (*E,Z*)-skipped diene side chain. Building on earlier work, the BC spiroacetal moiety would be installed through PMB deprotection/*in situ* spiroacetalisation of a *Z*-enone arising from coupling of the C1-C16 alkyne fragment **13** and C17-C40 aldehyde **14**.²⁶ Disconnection across C24-C25 *via* an sp^3 - sp^2 Suzuki coupling²⁹ then reveals two intermediates utilised previously, C17-C24 vinyl iodide **15** and C25-C40 *bis*-spiroacetal **16**.³⁰

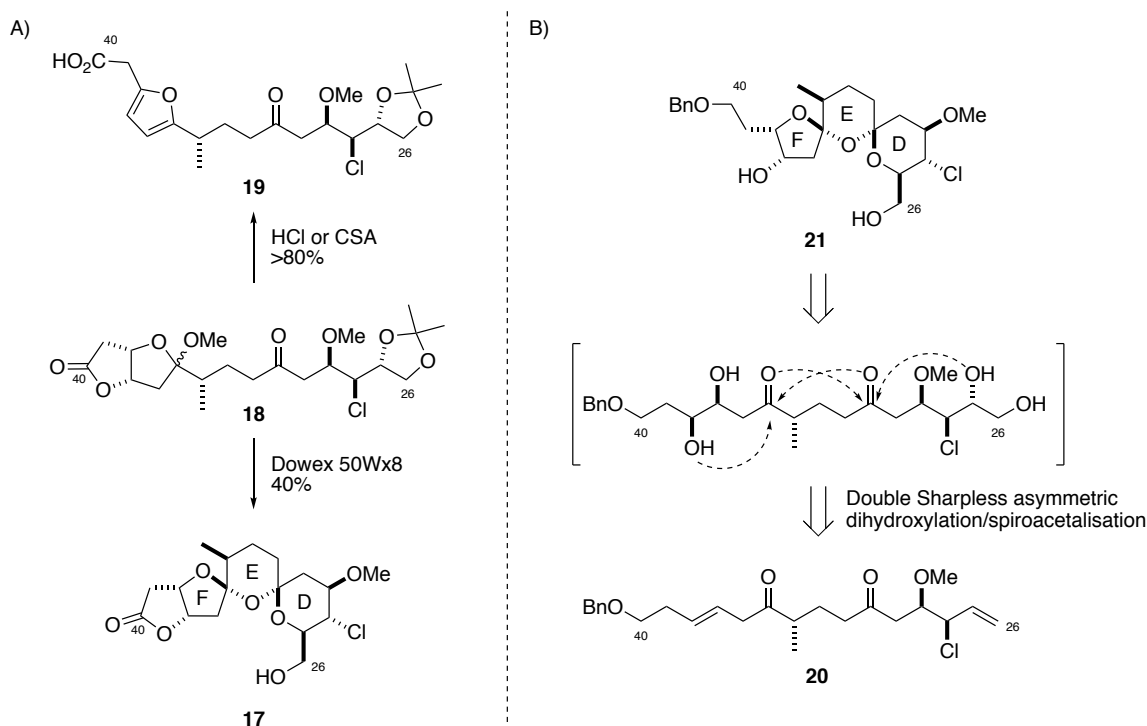


Scheme 2. Revised retrosynthesis of spirastrellolide A methyl ester (1)

In our first-generation synthesis, the construction of the C26-C40 DEF *bis*-spiroacetal

110 **17** *via* an acid-mediated deprotection/spiroacetalisation cascade of **18** was a major bottleneck.³¹ The problem stemmed from formation of the undesired furan **19** *via* competing elimination (**Scheme 3A**). Even after extensive optimisation, we could only generate a modest amount of the required C26-C40 DEF *bis*-spiroacetal **17**. Thus, we needed to revise our strategy in order to achieve a reliable multigram supply of this essential fragment. Firstly, we

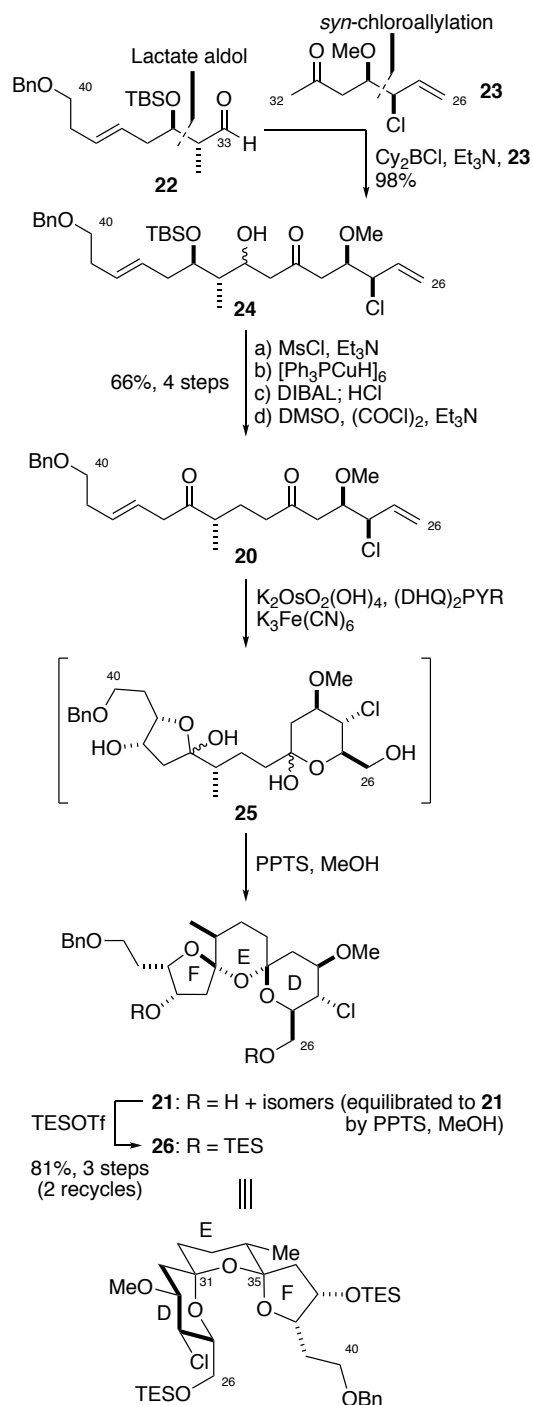
115 removed the appended γ -lactone in a bid to avoid competitive furan formation. Additionally,
 we noted that the *bis*-spiroacetal could arise from a tetraol linear precursor. In particular, we
 recognised that the sense of asymmetric induction *via* the Sharpless asymmetric
 dihydroxylation required to install the C37/C38 and C26/C27 hydroxyls was the same. This
 led to an adventurous double dihydroxylation/spiroacetalisation cascade as in **20** to **21**, which,
 120 if successful, would provide an elegant and efficient synthesis of the DEF *bis*-spiroacetal ring
 system (**Scheme 3B**).



Scheme 3. A) First-generation approach towards the C26-C40 DEF *bis*-spiroacetal **17**. B) Revised strategy towards the C26-C40 DEF *bis*-spiroacetal **21**

The required linear precursor **20** (**Scheme 4**) was readily prepared from aldehyde **22** and ketone **23**, notably employing an Oehlschlager-Brown *syn*-choroallylation³² and our lactate aldol methodology³³ to set up the required stereocentres.²⁴ A boron-mediated aldol reaction facilitated the fragment union to form β -hydroxyketone **24**, which led onto the required linear precursor **20** *via* a four-step sequence.³⁰ At this stage, we attempted the pivotal double

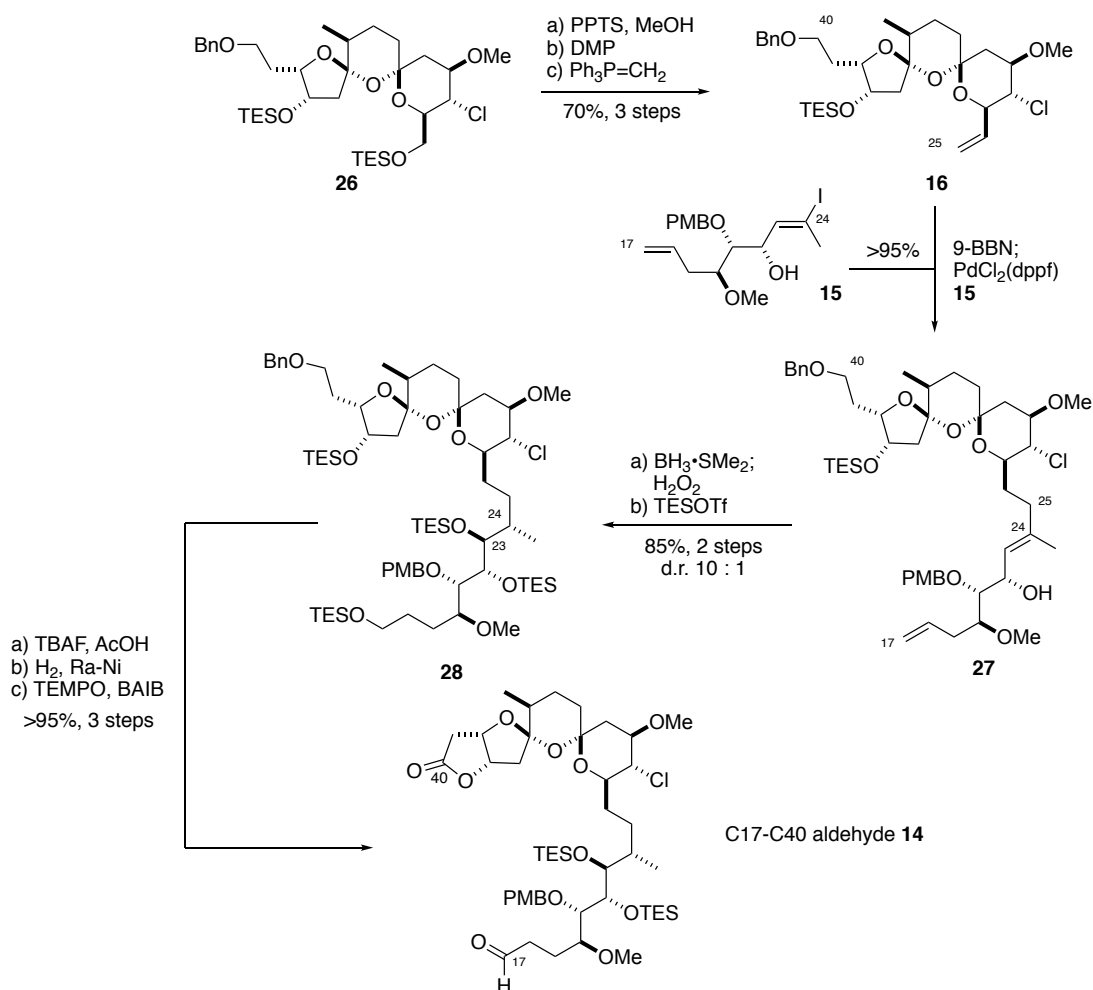
asymmetric dihydroxylation.³⁴ This initially afforded *bis*-hemiacetal **25**, which to our delight spirocyclised under mild acidic conditions to afford the DEF-*bis*-spiroacetal **21**. Fortuitously, we discovered that other spirocyclic isomers of **21** could be resubmitted under acidic conditions to afford the required DEF *bis*-spiroacetal cleanly. This was only made possible by
135 the increased stability of the DEF *bis*-spirocycle circumventing furan formation, giving us the opportunity to employ thermodynamic equilibration rather than kinetic control. A final *bis*-silylation delivered the protected fragment **26** efficiently. Most importantly, this route facilitated a dependable multigram scale synthesis of the crucial C26-C40 *bis*-spiroacetal moiety.



Scheme 4. Revised synthesis of the C26-C40 DEF *bis*-spiroacetal **26**

Armed with an efficient and scalable route towards C1-C16 alkyne **13**, C17-24 vinyl iodide **15** and now the C26-C40 *bis*-spiroacetal **26**,^{26,30} we set out to improve the fragment coupling sequence (**Scheme 5**).³⁵ Preparation of C17-C40 aldehyde **14** commenced with a primary TES deprotection, oxidation and methylenation to provide the corresponding C25-

C40 alkene **16**. Hydroboration of **16** followed by an *in situ* sp^3 - sp^2 Suzuki cross-coupling with vinyl iodide **15** forged the C24-C25 bond and furnished diene **27** cleanly.^{29,36} The final two stereocentres of the C17-C40 fragment were set up *via* a diastereoselective substrate-controlled double hydroboration sequence; installing the C17 and C23 hydroxyl groups and affording the required 23,24-*anti* stereochemistry in **28**. Protecting group manipulations then yielded an advanced triol, which was subjected to a selective triple oxidation of the two primary alcohols with concomitant lactonisation to afford the required C17-C40 aldehyde **14**.



Scheme 5. Synthesis of the C17-C40 aldehyde **14**

Our initial coupling strategy to form the C16-C17 bond hinged upon the addition of an alkynyllithium species to the C17 aldehyde.²⁶ However, this transformation now proved to

160 be capricious owing to competing addition to the γ -lactone moiety. Instead, a Nozaki-Hiyama-Kishi coupling^{37,38} between iodoalkyne **29** and aldehyde **14**, to our delight, chemoselectively and reliably forged the C16-C17 bond (**Scheme 6**). The BC spiroacetal formation commenced with a Lindlar reduction of the alkyne **30** and oxidation to the *Z*-enone. Subsequent *bis*-PMB deprotection under controlled conditions set the scene for a concomitant acetalisation to
165 cleanly forge the BC-spiroacetal ring system, now affording **31** with all the requisite ABCDEF rings in a stereodefined manner. With the carbon and oxygen skeleton for the macrocycle now in hand, our attention turned towards side chain installation and the final macrolactonisation. A selective primary TBS ether deprotection, partial reduction of the γ -lactone and vinylation afforded allylic alcohol **32**, which was then treated with triphosgene to both temporarily mask
170 the diol as well as providing the requisite leaving group for the π -allyl Stille cross-coupling. Pleasingly, the planned cross-coupling between allylic carbonate **11** and vinyl stannane **12** proceeded efficiently, and was a major improvement over our previous cross-metathesis route in the presence of the full macrocycle. With only the macrolactonisation and global deprotection left, the finish line was now in sight. Once again, this transformation proved to
175 be significantly more challenging than initially anticipated!

(**Scheme 7A**). This unexpected difficulty was in stark contrast to the highly efficient macrolactonisation (>95%) observed in our first-generation route (**Scheme 7B**), which we attributed to a degree of favourable conformational pre-organisation in the *seco*-acid **34**. Comparison of the *seco*-acid **10** with that used previously highlighted only one seemingly minor structural difference – the (very distal) C23 TES ether. Therefore, we hypothesised that unfavourable conformational effects, presumably imposed by the additional silyl protecting group, were operating to bias the free acid away from ring closing with the C37 alcohol. As such, we treated *seco*-acid **10** with PPTS in methanol to effect controlled *mono*- and *bis*-TES ether cleavage. Our hypothesis was proven to be correct; submitting either of the *mono*- or *bis*-desilylated products (**35** and **36**) to standard Yamaguchi macrolactonisation conditions now afforded macrocycles **37** and **38** in excellent yield (**Scheme 7C**). A final global deprotection completed our second-generation synthesis of spirastrellolide A methyl ester (**1**) in 23 linear steps and 6% overall yield from C26-C40 *bis*-spiroacetal **26**. When compared with the first-generation synthesis (25 steps and 1% overall yield), it is pleasing to note the improvement in efficiency, both in terms of step count and yield. Moreover, we discovered that we were incredibly lucky in our first-generation synthesis – where the troublesome C23-TES ether was unintentionally cleaved in the BC-spiroacetalisation step, which greatly assisted the crucial downstream macrolactonisation reaction. An important lesson was learned here, that protecting groups can have subtle and unpredictable conformational effects in such complex substrates!

210 **Leiodermatolide**

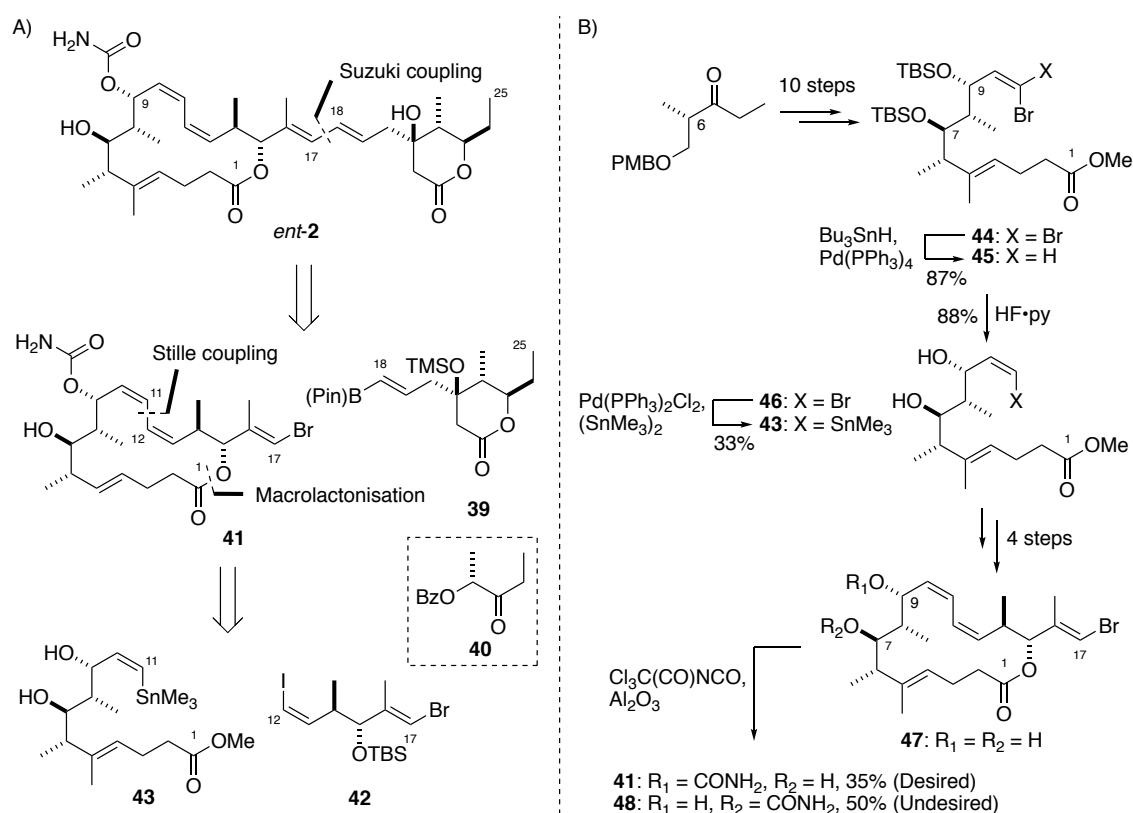
In 2008, leiodermatolide (**2**) was isolated from the lithistid sponge *Leiodermatium* sp. collected off the coast of Florida by the Wright group.⁴¹ Spectroscopic analysis illuminated the planar structure of **2** and revealed a 16-membered macrolactone containing a *Z,Z*-diene and a pendant carbamate group, as well as an *E,E*-diene on the side chain terminating in a δ -
215 lactone. The assigned structure highlighted the presence of nine stereocentres; six of which lie in the macrocycle and three in the terminal δ -lactone.⁴² Biological evaluation showed that leiodermatolide exhibited potent anticancer activity, in particular against a range of drug-resistant cancer cell lines. While leiodermatolide-treated cells exhibited physiological responses often typified by tubulin-binding compounds, *in vitro* studies failed to show
220 evidence for any direct tubulin interaction. As such, it was suggested that leiodermatolide acted *via* an indirect mechanism orthogonal to other known tubulin-targeting anticancer drugs, indicative of a promising anticancer drug candidate.

Our involvement with leiodermatolide was borne from its initially inconclusive stereochemical assignment. In collaboration with the Wright group, extensive NMR
225 spectroscopic analysis, molecular modelling and computational DP4 NMR predictions⁴³ allowed us to refine the structure to a single diastereomer for the C1-C16 macrocycle and the C21-C25 δ -lactone with >99% probability. Unfortunately, the distal nature of the C21-C25 δ -lactone relative to the macrocycle precluded a conclusive determination of the stereochemistry between these two stereoclusters, leading to four candidate stereoisomers for the natural
230 product. To definitively pin down the stereochemistry of **2**, we embarked on a synthetic campaign geared towards confirming the 3D structure of the macrocycle followed by the full natural product. A synthesis-enabled stereochemical elucidation was a notion shared with other research groups,^{44,45} which, to date, has resulted in one other group successfully synthesising leiodermatolide.^{46,47}

235 As the absolute configuration was unknown, we arbitrarily targeted *ent*-**2** and its diastereomer for initial studies. Our initial approach towards **2** hinged upon a late-stage sp^2 - sp^2 Suzuki coupling across C17-C18 to allow the flexible appendage of both enantiomers of the C18-C25 δ -lactone to the macrocycle, as shown in **Scheme 8A**. The C18-C25 δ -lactone **39** could be readily synthesised from either enantiomer of **40**. We anticipated that the C1-C17
240 macrocycle **41** could be constructed from a linchpin *bis*-halide fragment **42**, leveraging the more reactive vinyl iodide to selectively engage in a Stille cross-coupling with C1-C11 vinyl stannane **43**.

In executing this approach (**Scheme 8B**), we discovered that the *bis*-TBS protection of the C7 and C9 hydroxyl groups required relatively forcing conditions to effect the second
245 silylation at C7.⁴⁸ This observation indicated the possibility of realising a site-selective C9 carbamate installation in the endgame. Our resulting synthesis of the C1-C17 macrocycle **41** confirmed our relative stereochemical assignment through spectroscopic correlations.⁴⁸ However, the specific rotation recorded for the macrocycle was opposite in sign to (–)-leiodermatolide; tentatively suggesting that we may have embarked in the wrong enantiomeric
250 series. Additionally, there were two key issues we needed to address in the evolution of our synthetic strategy. Firstly, while the semi-reduction of vinyl dibromide **44** to (*Z*)-vinyl bromide **45** proceeded smoothly, subsequent attempts at converting it into the vinyl stannane proved problematic. This involved cleavage of the C7 and C9-TBS ethers to afford diol **46**, followed by stannylation under Wulff-Stille conditions⁴⁹ to form stannane **43**, albeit in a
255 modest yield (**Scheme 6B**). Furthermore, despite preliminary results suggesting otherwise, our vision of a late-stage site-selective carbamate installation proved unrewarding; treatment of the macrocycle **47** with trichloroacetyl isocyanate⁵⁰ resulted in a 3 : 2 mixture of regioisomeric products **41** and **48** that favoured the undesired C7 carbamate **48**. Moreover, attempts at realising the key Suzuki coupling to afford the full leiodermatolide carbon skeleton

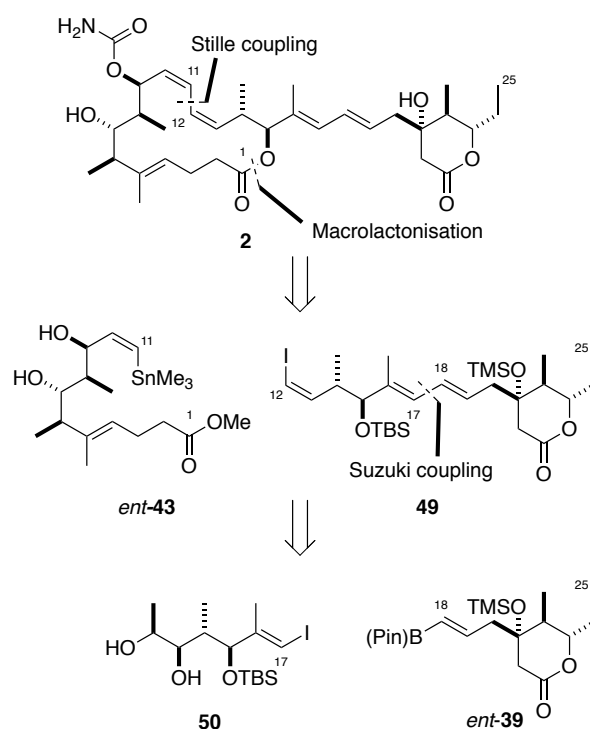
260 proved fruitless; vinyl bromide **41** was found to be unreactive under a variety of palladium-catalysed conditions.⁵¹



Scheme 8. A) Initial approach towards leiodermatolide (*ent-2*). B) Summary of our first-generation synthesis towards the C1-C17 macrocycle **41**

265 This intelligence gathering exercise prompted us to revise our synthetic strategy towards **2**, as highlighted in **Scheme 9**, and we instead looked towards forming the fully elaborated macrocycle *via* a late-stage macrolactonisation. As the C11-C12 bond was reliably installed *via* a Stille coupling, we sought to disconnect the molecule into the C1-C11 vinyl stannane *ent-43* and the C12-C25 δ -lactone **49**. The C12-C25 fragment itself can then be constructed

270 from vinyl iodide **50** and δ -lactone *ent-39*, employing a Suzuki coupling to forge the C17-C18 bond. Despite disappointing initial results, we remained optimistic about effecting a regioselective carbamate formation, thereby minimising protecting group manipulations.



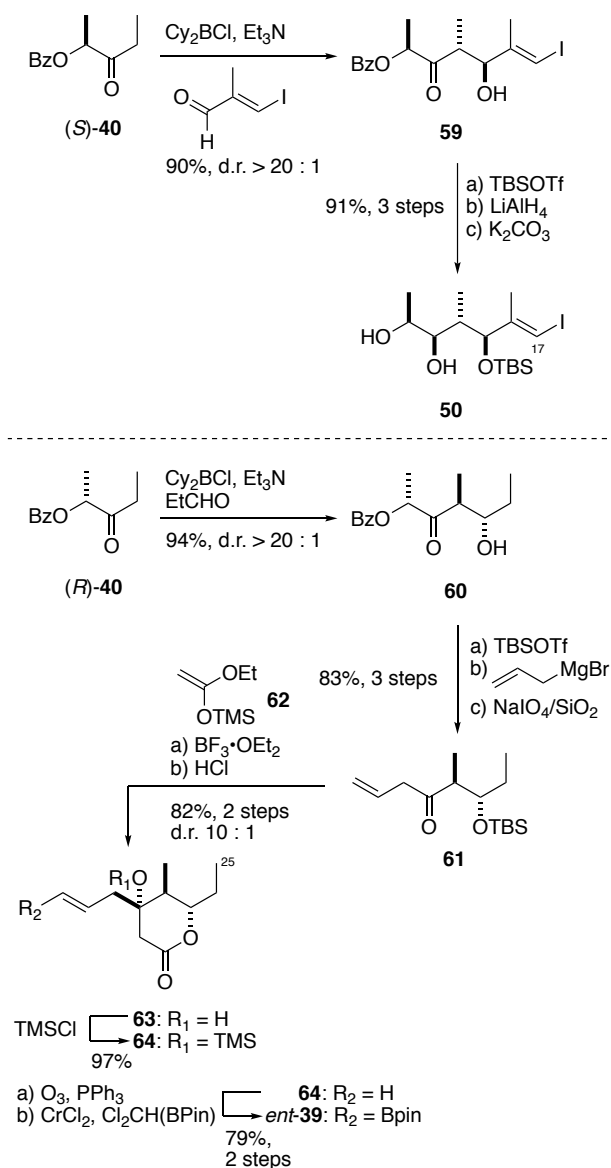
Scheme 9. Revised retrosynthesis for leiodermatolide (**2**)

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Our revised synthesis of the C1-C11 stannane *ent*-**43** commenced from the Weinreb amide **51** derived from (*R*)-Roche ester (**Scheme 10**). By trapping the kinetic *Z*-enolate of the derived ketone with Comins' reagent⁵² followed by a Suzuki-type methylation of vinyl triflate **52**, we successfully formed the trisubstituted alkene **53**.⁵³ Employing methodology developed by our group, a lactate aldol reaction between (*R*)-lactate-derived ethyl ketone (*R*)-**40** and aldehyde **54** readily afforded the required *anti* adduct **55** with excellent diastereoselectivity.^{33,54,55} A four-step sequence installed the requisite alkyne and removed the lactate auxiliary. The required 1,3-*anti* reduction on ynone **56** proved problematic; employing the Evans-Tishchenko⁵⁶ protocol failed outright. Unfortunately, the Evans-Saksena reduction⁵⁷ on the same substrate gave poor diastereoselectivity. This was rationalised based on the small size of the alkyne substituent, reducing its preference to occupy the equatorial position in the transition state. Based on this hypothesis, we looked towards increasing the steric bulk by preparing the *Z*-vinyl iodide **57**.⁵⁸ Luckily, this drastically improved the

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silyl ketene acetal **62**.^{8,60} This, followed by an acid-mediated lactonisation, delivered the δ -lactone **63**, where the matched stereoinduction from 1,2-Felkin and 1,3-Evans polar models are mutually reinforcing.⁶¹ Subsequent silylation afforded the protected lactone **64**, where a
 305 two-step sequence revealed the required vinyl boronate *ent*-**39** in anticipation for the key cross-coupling.

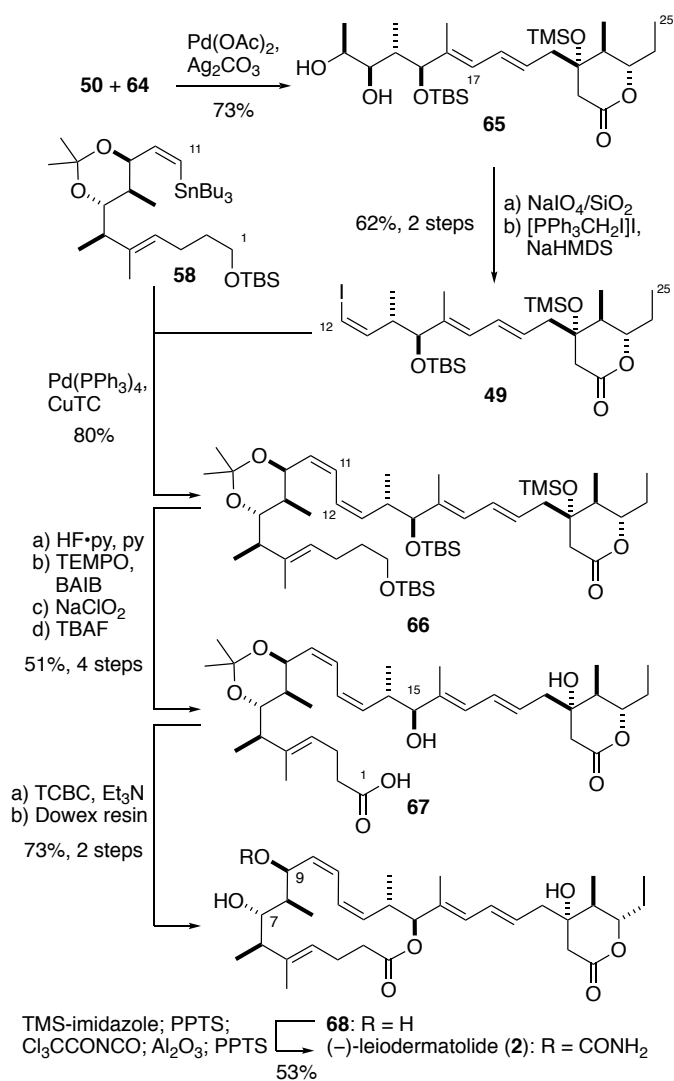


Scheme 11. Synthesis of the C12-C17 vinyl iodide **50** and C18-C25 δ -lactone *ent*-**39**

310 The planned Suzuki coupling could be effected between vinyl iodide **50** and vinyl boronate *ent*-**39**. Advantageously, we discovered that the fragment union could also be readily

achieved with excellent geometrical control *via* the Heck reaction to deliver **65** (Scheme 12),⁶² saving two steps in converting the alkene **64** to the vinyl boronate *ent*-**39** (*vide supra*). A two-step procedure revealed the required C12-C25 vinyl iodide **49**, which underwent a facile Stille coupling^{63,64} with stannane **58** to establish **66**, corresponding to the full carbon skeleton of leiodermatolide. Finally, a series of redox and protecting group manipulations revealed the *seco*-acid **67**, which was efficiently macrocyclised under our preferred Yamaguchi conditions³⁹ to generate the 16-membered macrolactone.

With a global deprotection revealing the *des*-carbamoyl derivative of leiodermatolide **68**, all that was required was the pivotal regioselective C9 carbamoylation. We surmised that the steric hindrance around C7 should heighten the reactivity of the C9 alcohol, a rationale supported by molecular modelling studies. As previously alluded to, treating the truncated macrolactone **47** with trichloroacetyl isocyanate⁵⁰ favoured the formation of the undesired C7 carbamate **48**, with extensive experimentation failing to overturn this result. Interestingly enough, we observed that esterification or silylation proceeded with high selectivity at the C9 position. This hinted that it was indeed the more reactive position, with the carbamoylating agent behaving anomalously. Leveraging this finding, a sequence involving *bis*-silylation, selective C9 desilylation, followed by treatment with trichloroacetyl chloride and C7 desilylation successfully led to (–)-leiodermatolide (**2**) in 23 steps and 3.2% overall yield.⁵⁹ Careful comparison with the authentic sample provided by the Wright group confirmed that they were identical in all respects. Serendipitously, this 3D structure corresponds exactly to the one out of four stereoisomers arbitrarily rendered in our isolation paper.⁴² At this point, we could embark on a programme of SAR studies and further biological evaluation of this promising anticancer lead structure.⁶⁵



Scheme 12. Fragment union and completion of (-)-leiodermatolide (**2**)

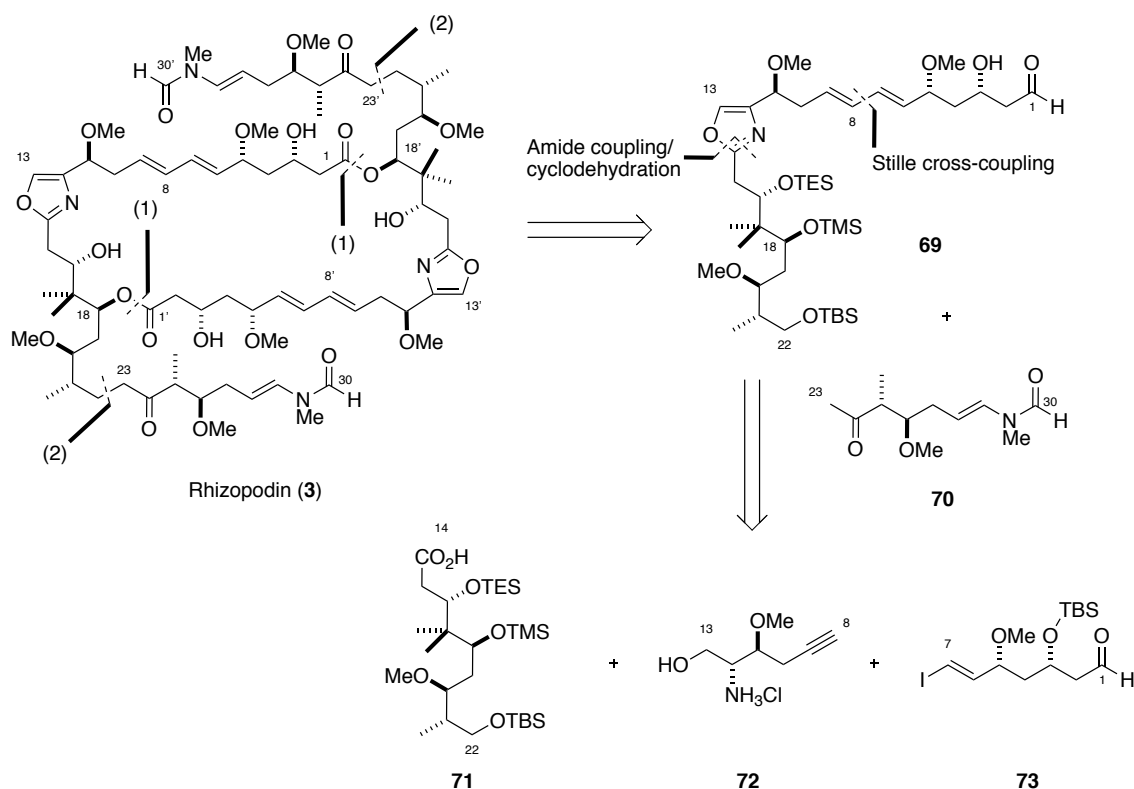
Rhizopodin

Rhizopodin (**3**) is an architecturally complex macrocyclic polyketide first isolated in 1993 by Höfle and Reichenbach from the myxobacterium *Myxococcus stipitatus*.⁶⁶ By binding with and inhibiting actin polymerisation, rhizopodin mediates potent antiproliferative activity as well as strong cytostatic effects against a range of cancer cell lines.⁶⁷ This selective interaction with actin also enabled its structural elucidation, with X-ray crystallographic studies of the bound rhizopodin-actin complex revealing an intriguing C_2 -symmetric macrodiolide.⁶⁸ From a structural perspective, 14 of the 18 stereocentres are embedded in the 38-membered macrolide core, together with two oxazole rings and two diene motifs, with the remaining four stereocentres located on the two side chains.⁶⁹ The ornate architecture and promising anticancer profile of rhizopodin has rendered intensive research towards its total synthesis. Although several groups have reported the synthesis of various substructures,^{70–74} there has only been two completed total syntheses of the target structure itself.^{75–77}

Our proposed synthesis (**Scheme 13**) of rhizopodin (**3**) centred on structural simplification into the truncated monomer **69** and known side chain fragment **70**.⁷⁸ This disconnection provided a degree of flexibility, with macrocycle formation possible *via* direct or sequential esterification, followed by bidirectional aldol coupling with ketone **70** to incorporate the requisite side chain(s). Oxazole formation was envisaged *via* amide bond formation between C14-C22 acid **71** and C8-C13 amino alcohol **72** followed by dehydration, while diene installation was proposed using a Stille coupling of vinyl iodide **73** and a suitable C8 stannane.

As is often the case with complex polyketide synthesis, the strategic incorporation of orthogonal protecting groups was of crucial importance. Initially, we envisaged incorporating PMB ethers to chemoselectively unmask the required alcohols for the macrolactonisation and side chain attachment. However, we found that an oxidative PMB ether cleavage using DDQ

resulted in the concomitant oxidation of the C5 allylic methyl ether, with alternative Lewis
 365 acidic cleavage degrading our advanced intermediates.⁷⁷ As such, we opted for a carefully
 selected combination of silyl protecting groups. Notably, attempts at deprotecting the C16-
 OTBS ethers in the endgame resulted solely in eliminated product. Frustratingly also, attempts
 at deprotecting a primary C22-OTIPS ether to allow side-chain installation, in the presence of
 a secondary C16-OTES ether, resulted in simultaneous cleavage of both silyl groups. These
 370 difficulties ultimately forced us to opt for a riskier gamut of silyl protecting groups in acid **71**
 and aldehyde **73** (*vide infra*).



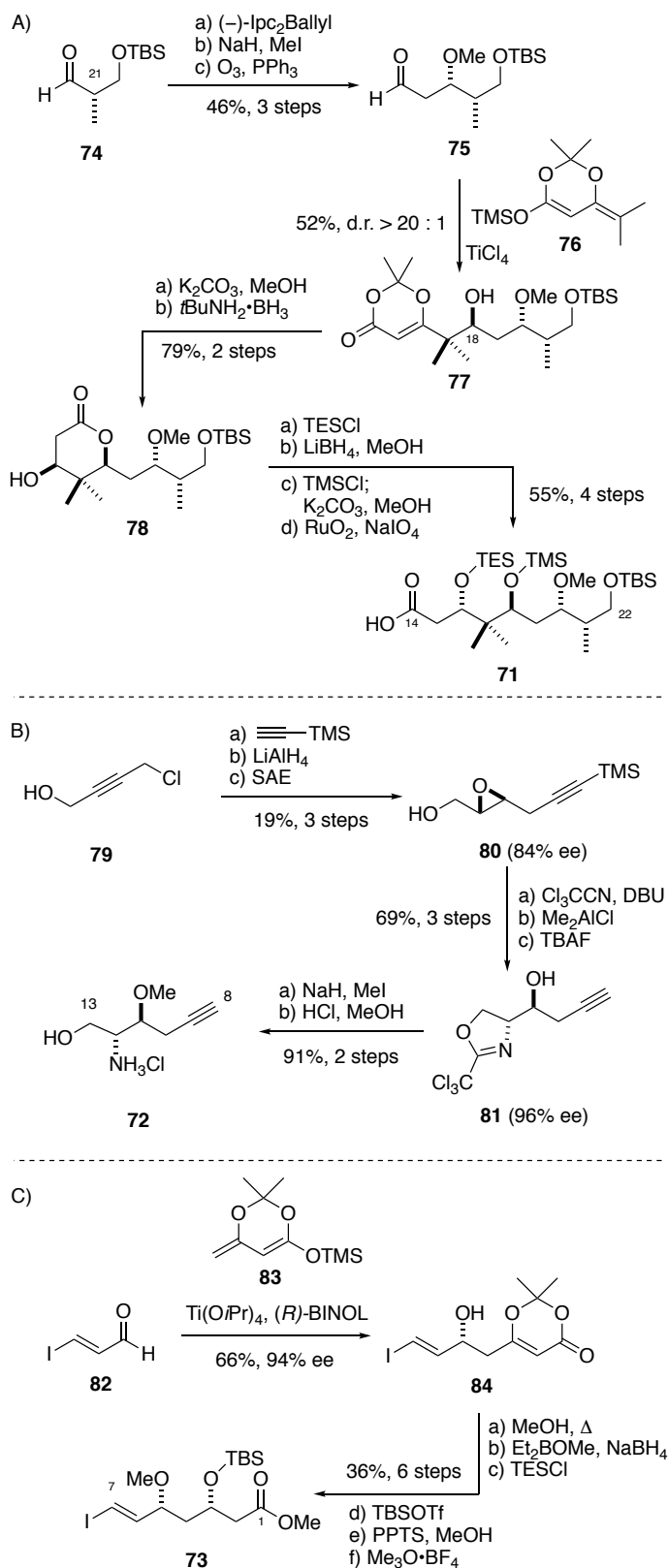
Scheme 13. Retrosynthetic analysis of rhizopodin (**3**). Disconnection (1) refers to an esterification/macrolactonisation, disconnection (2) refers to an aldol/dehydration/reduction sequence

375 Synthesis of the C14-C22 carboxylic acid **71** commenced with a Brown allylation onto
 Roche ester-derived aldehyde **74** (**Scheme 14A**).⁷⁹ The remaining stereocentres in this
 fragment were generated first *via* a Mukaiyama aldol reaction between aldehyde **75** and silyl
 ketene acetal **76**, setting up the C18 stereocentre, and a subsequent diastereoselective
 reduction⁸⁰ of the cyclic ketone after methanolysis of dioxinone **77**. From β -hydroxylactone

380 **78**, subsequent protections and oxidation afforded the C14-C22 acid **71**. The amino-alcohol coupling partner **72** required for the oxazole formation was formed from propargyl alcohol **79** (**Scheme 14B**). A Sharpless asymmetric epoxidation (yielding epoxide **80**)^{81,82} followed by amidation and regioselective epoxide opening gave oxazoline **81**. A final sequence of methylation and hydrolysis then delivered the amino alcohol **72**.

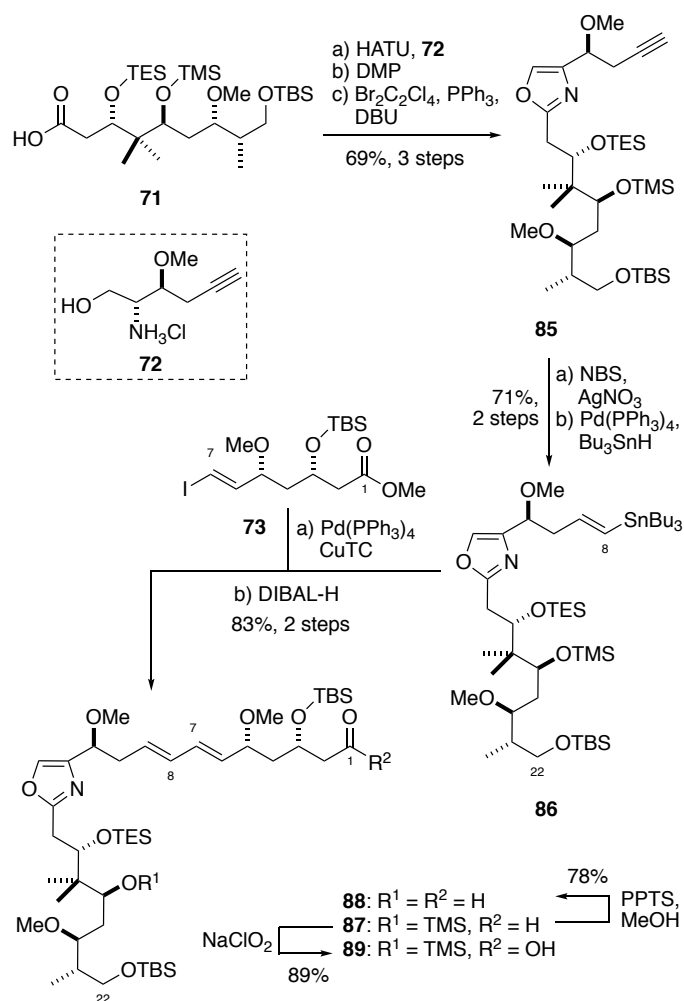
385 The final C1-C7 fragment **73** required for the macrocycle was obtained by an enantioselective Mukaiyama aldol reaction between aldehyde **82** and Chan's diene (**83**) (**Scheme 14C**).^{83,84} Subsequent methanolysis of dioxinone **84** followed by a Narasaka reduction⁸⁵ generated the free diol. Protecting group manipulations and a final methylation of the free C5-OH then afforded the required Stille coupling partner **73**.

390



Scheme 14. A) Synthesis of the C14-C22 carboxylic acid **71**. B) Synthesis of the C8-C13 amino alcohol **72**. C) Synthesis of the C1-C7 vinyl iodide **73**

Fragment assembly commenced with an amide bond formation between carboxylic acid
395 **71** and amino alcohol **72** (**Scheme 15**). Employing modified Robinson-Gabriel conditions
developed by Wipf,⁸⁶ oxazole **85** was formed cleanly. Subsequent stannylation afforded vinyl
stannane **86**, which was coupled with vinyl iodide **73** *via* a Stille cross-coupling⁶³ to give the
truncated monomer in anticipation for the key macrocyclisation step. At this stage, we
discovered that a series of oxidation state adjustments and protecting group manipulations
400 were critical for the success of the macrocycle formation. While conditions required for
methyl ester hydrolysis concomitantly unmasked the required C18-OH, Yamaguchi
macrolactonisation conditions³⁹ disappointingly afforded a mixture of oligomers, primarily
corresponding to the monomeric truncate. As such, we were forced to adopt a stepwise
approach to access both coupling partners for the macrolactonisation. A controlled reduction
405 to the aldehyde **87** therefore was performed, meaning that this key intermediate could be
subjected to either a controlled C18-OTMS desilylation (**88**) or a Pinnick oxidation to afford
seco-acid **89**.



Scheme 15. Synthesis of the truncated C1-C22 monomers

410

Following these manoeuvres, a selective esterification between alcohol **88** and *seco*-acid **89** served to complete the linear carbon skeleton in **90** (**Scheme 16**). This was followed by a similar sequence of desilylation, oxidation and macrolactonisation to close the required macrocycle **91**. The C₂-symmetry of the molecule presented the opportunity of performing a

415 bidirectional side-chain installation in the endgame. This required a selective C22-22' primary TBS ether cleavage, a capricious operation owing to the presence of multiple secondary silyl protecting groups of similar lability. In the end, carefully controlled exposure of the protected macrocycle **91** to HF/py selectively afforded the C22/22' diol **92** which, following oxidation, underwent a double boron-mediated aldol addition with ketone **70**.⁷⁸ Drawing from our

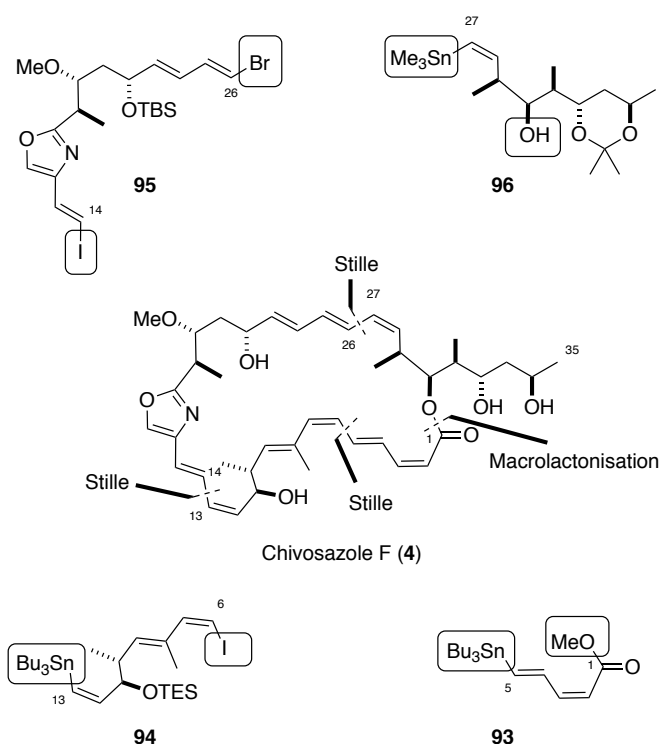
420 reidispongioid synthesis,⁷⁸ a sequence involving a controlled dehydration,⁸⁷ followed by a

Chivosazole F

430 Following their discovery of rhizopodin, Höfle and Reichenbach reported the isolation of chivosazoles A-F from the myxobacterium *Sorangium cellulosum* in 1995.^{88,89} The chivosazoles are a structurally unprecedented class of polyene macrolides, with each member of the family differing in terms of the substitution at C11 and C20. Notably, the chivosazole family displayed potent inhibitory activity against filamentous fungi, yeast and a panel of
435 human cancer cell lines. This bioactivity stems from its selective inhibition of actin polymerisation. Intriguingly, the lack of structural homology to other known actin-binders suggests that the chivosazoles may have a distinct mode of action.^{90,91} What ignited our interest in the chivosazoles as a synthetic target was their astounding array of structural features (**Scheme 17**). Specifically, all congeners as typified by chivosazole F (**4**) possess a
440 31-membered macrolactone, containing 10 stereocentres and an oxazole moiety. However, the most impressive feature is the set of conjugated polyenes with alternating geometry in the macrocycle: a (Z,E,Z,E)-C2-C9 tetraene, a (Z,E)-C12-C15 diene and an (E,E,Z)-C23-C28 triene regions.⁹² These polyene regions demanded careful handling of sensitive late-stage intermediates and mild reaction conditions, necessary to suppress both potential olefin
445 isomerisation and degradation pathways. Perhaps as a reflection of the challenges imposed by this demanding target, only two total syntheses of chivosazole F (**4**), including our approach described below, have been reported to date.^{93,94}

Our synthetic approach needed to address the delicate nature of the chivosazole structure; in particular, the isomerisation-prone (2Z,4E,6Z,8E)-tetraene. Therefore, we sought
450 to minimise the number of endgame transformations. To this end, we envisaged a highly convergent approach towards accessing the full carbon skeleton by employing site-selective cross-couplings. This broadly disconnects the full carbon skeleton to reveal the C14-C35 northern hemisphere and the C1-C13 southern hemisphere of the natural product.

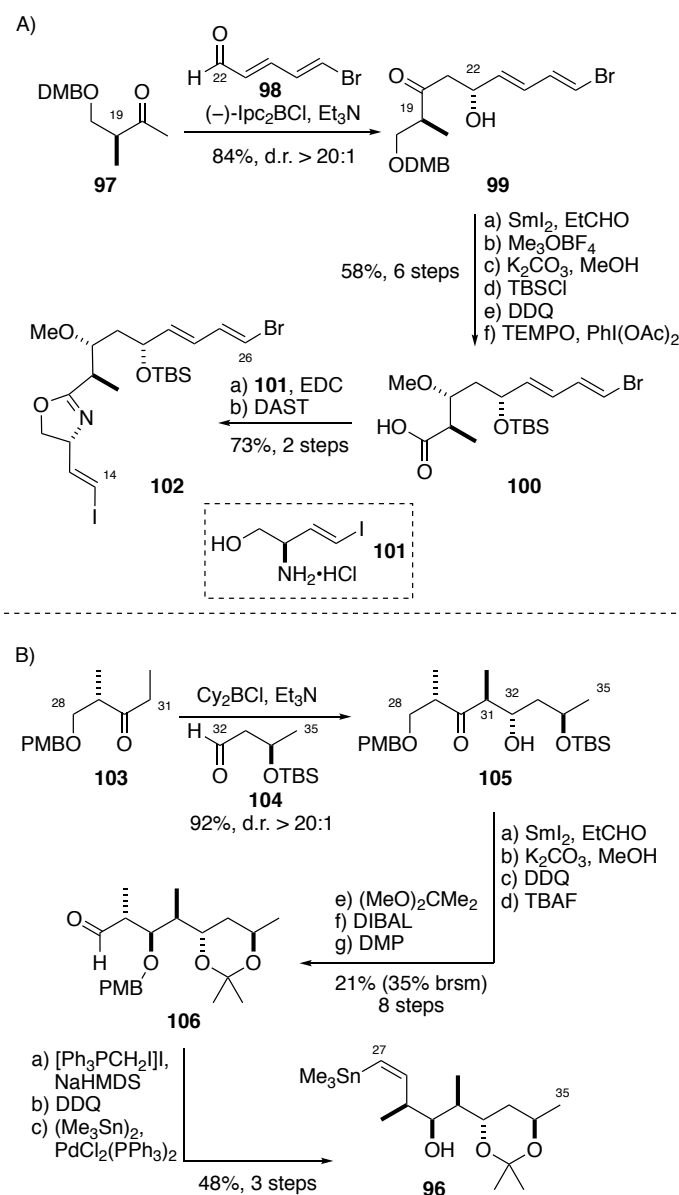
The success of this strategy crucially relied on the judicious choice of coupling handles and cross-coupling conditions. Building on initial intelligence gathering studies, we discovered that the Stille cross-coupling provided the most efficient means of fragment union. We also anticipated that a late-stage macrolactonisation might generate the macrocycle. This analysis revealed four constituent fragments – the C1-C5 fragment **93**, the C6-C13 fragment **94**, the C14-C26 fragment **95** and the C27-C35 fragment **96**.



Scheme 17. Initial synthetic strategy towards chivosazole F (**4**) and the four proposed fragments

Recognising the 19,22-*syn* relationship, synthesis of the C14-C26 *bis*-halide linchpin commenced with an asymmetric boron-mediated aldol reaction from methyl ketone **97** and aldehyde **98**^{95,96} to afford β -hydroxyketone **99** (**Scheme 18A**). This was then subjected to Evans-Tishchenko reduction⁵⁶ to establish the remaining stereocentre. The oxazoline ring was cyclised using DAST⁹⁷ following amide formation from carboxylic acid **100** and amino alcohol **101**.⁹⁸ From oxazoline **102**, oxazole formation using MnO₂ proved incompatible with the pendant vinyl iodide functionality, suggesting that this oxidation step should be conducted post-fragment assembly. Beginning from the ethyl ketone derivative **103** of (*S*)-Roche ester

470 and known aldehyde **104**,^{99,100} a boron-mediated aldol reaction¹⁰¹ readily installed the C31 and C32 stereocentres in β -hydroxyketone **105**, with an Evans-Tishchenko reduction again employed to set the final C30 stereocentre (**Scheme 18B**). A six-step sequence revealed aldehyde **106**, which was subjected to a Stork-Zhao olefination, deprotection and stannylation to afford the required stannane **96**.⁴⁹

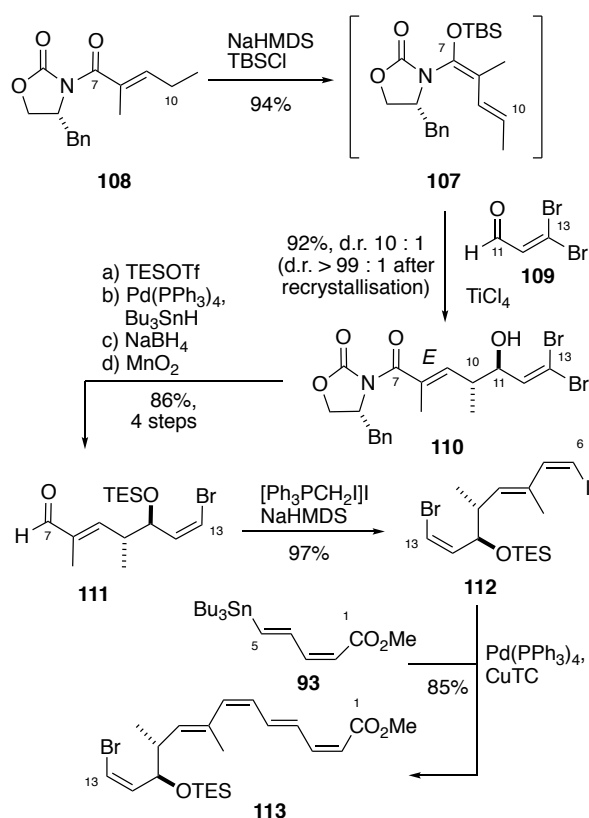


Scheme 18. A) Synthesis of the C14-C26 *bis*-halide linchpin **102**. B) Synthesis of the C27-C35 vinyl stannane **96**

The C1-C13 southern hemisphere contains what is arguably the most delicate polyene region of the chivosazoles. A vinylogous Mukaiyama aldol reaction¹⁰² between the chiral silyl

ketene aminal **107** (derived from imide **108**) with aldehyde **109** forged the two stereocentres in the C7-C13 fragment **110** (Scheme 19).¹⁰³ Subsequent Stork-Zhao olefination of aldehyde **111** installed the terminal (6*Z*)-vinyl iodide in **112**, which then engaged in a site-selective Stille cross-coupling with stannane **93** to afford the C1-C13 southern hemisphere **113** in preparation for exploring the planned fragment coupling sequence.

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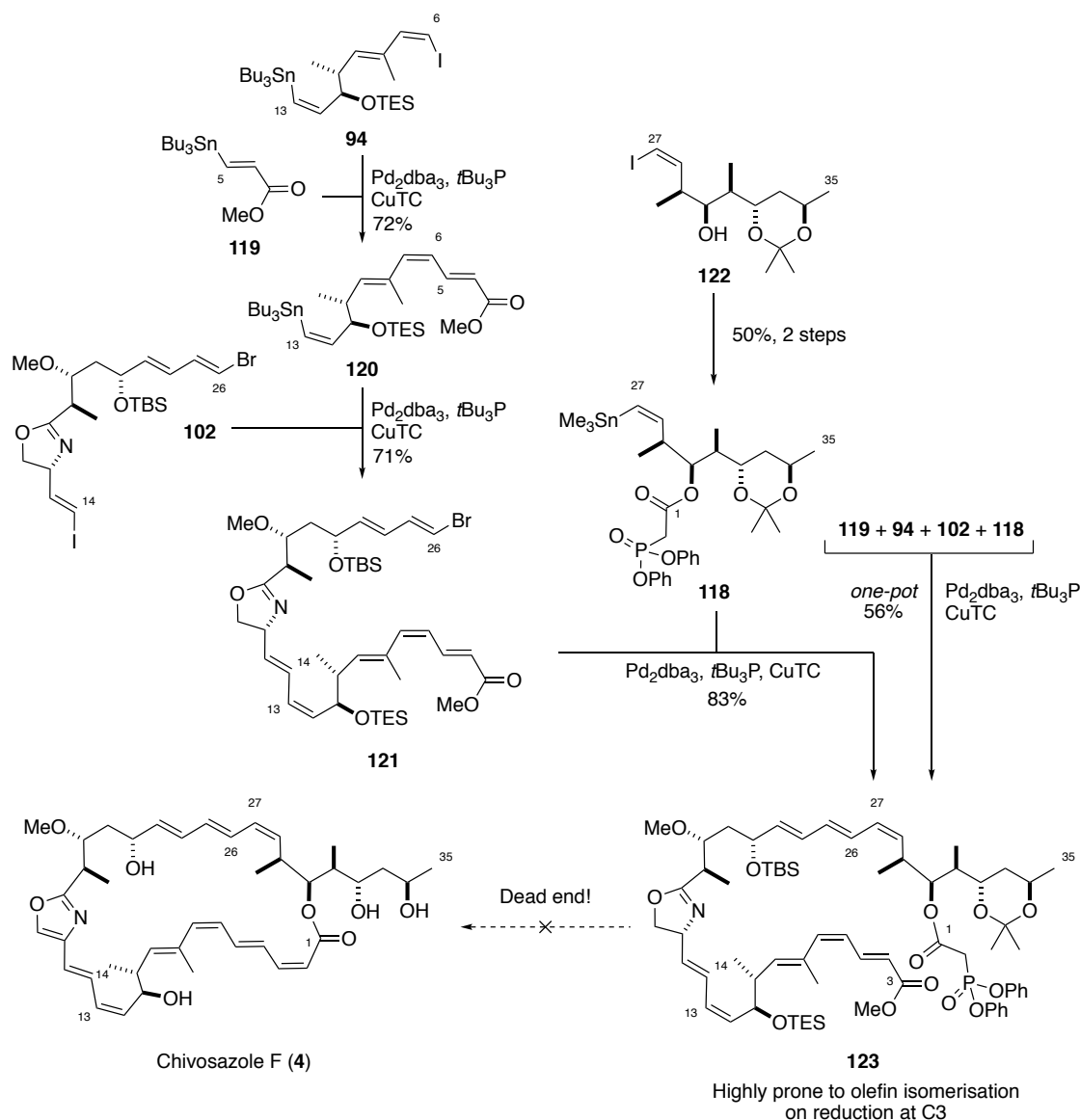


Scheme 19. Synthesis of the C1-C13 southern hemisphere fragment **113**

With the two hemispheres in hand, we looked towards effecting the site-selective Stille coupling between the stannane **114** derived from **113** and *bis*-halide **102**. Unfortunately, not only did this fail to effect the required coupling, it also highlighted the propensity for the tetraenoate **114** to isomerise under Pd(0) conditions (Scheme 20A). Similarly, model studies investigating the esterification of **115** with vinyl stannane **116**, with the goal of effecting a macro-Stille ring closure, afforded the isomerised (2*E*,4*E*)-stannane **117** under Yamaguchi

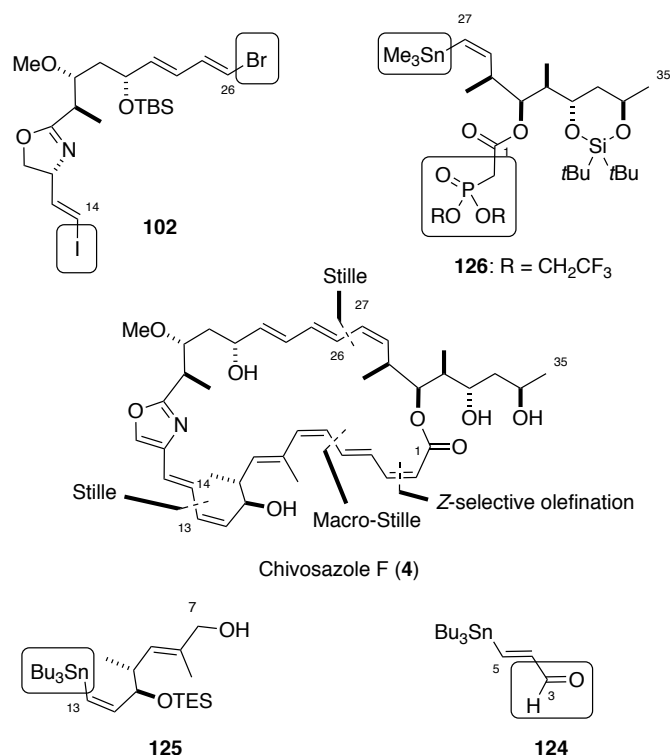
495 conditions (**Scheme 20B**). To avoid handling the isomerisation-prone (2*Z*) olefin, we next investigated the possibility of achieving a late-stage macro-olefination with a pendant phosphonate ester at C30 in **118**. The revised synthesis of the southern hemisphere thus involved a Stille coupling with vinyl iodide **94** and stannane **120** (**Scheme 20C**).

of $t\text{Bu}_3\text{P}^{104}$ was required to prevent isomerisation of the (6*Z*)-alkene. These conditions also allowed for the successful site-selective formation of the C13-C14 bond between *bis*-halide **102** and vinyl stannane **120**, as well elaborating the resulting vinyl bromide **121** with the C27-
510 C35 fragment **118** (derived from vinyl iodide **122**), with complete control of alkene geometry throughout the process. This success led us to ponder whether we could turn this into a one-pot process. Remarkably, with sequential addition of each fragment (i. **119**, ii. **94**, iii. **102** and iv. **118**), we were able to assemble the full carbon skeleton of the chivosazoles in **123** in one
515 pot in 56% yield (82% per coupling step). At this advanced stage, the (4*E*,6*Z*,8*E*)-triene was found to be highly prone to isomerisation on attempting to adjust the oxidation state at C3 ahead of the planned Horner-Wadsworth-Emmons (HWE) type macro-olefination. Furthermore, model studies on the planned Ando-olefination¹⁰⁵ gave poor control over the desired 2*Z* geometry. This series of disappointing and incredibly frustrating setbacks forced us to return to the drawing board...



Scheme 21. Employing the site-selective Stille coupling strategy to form the chivosazole backbone

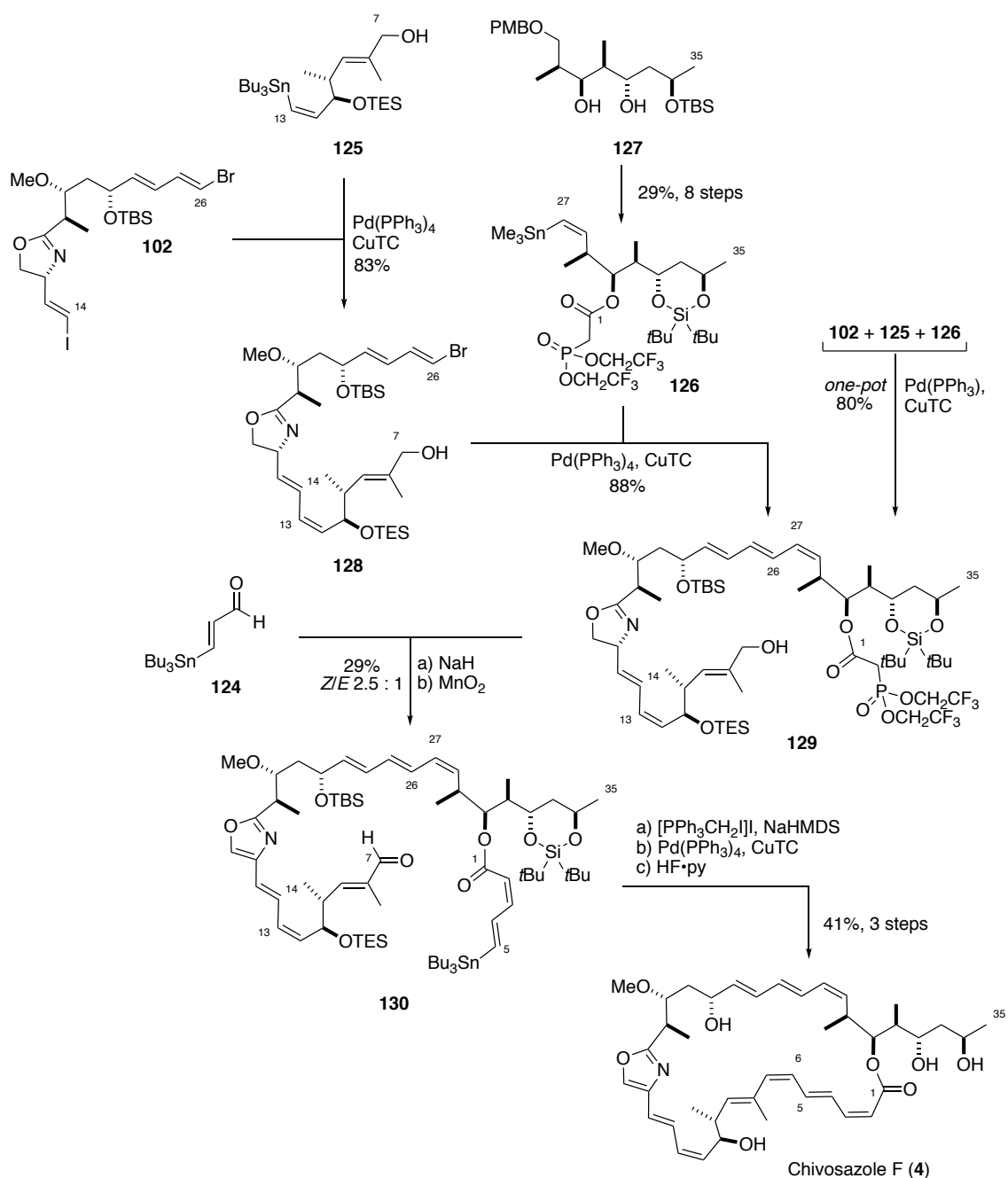
The challenges imposed by the delicate triene necessitated us to reconfigure our choreography of fragment coupling to an end-stage macro-Stille cyclisation (**Scheme 22**). Furthermore, to access the (2*Z*) geometry, an alternative olefination strategy was required. The anticipated lability of the target molecule also prompted us to switch from an acetonide to a silylene protecting group for the 32,34-diol to facilitate a mild final deprotection. These alterations meant that our constituent fragments towards assembling **4** would involve a C3-C5 aldehyde **124**, a revised C7-C13 stannane **125** and a revised C27-C35 phosphonate **126**.



Scheme 22. Final strategy adopted towards the total synthesis of chivosazole F (4)

The revised C27-C35 phosphonate **126** was made from diol **127**,⁹⁴ an intermediate used in our previous routes. Building on the prior work, fragment coupling could be conducted in a stepwise manner (*via* the C7-C26 vinyl bromide **128**) or a one-pot process (i. **102** ii. **125** iii. **126**) to efficiently deliver the advanced fragment **129** (Scheme 23). Gratifyingly, employing the Still-Gennari type phosphonate afforded useful selectivities towards the desired 2*Z* geometry for the HWE olefination with aldehyde **124**.^{106,107} At this stage, a double oxidation of the C7-OH and the oxazoline was carried out using MnO₂, notably accomplishing the challenging aromatisation on a delicate advanced fragment. Subsequently, the resulting aldehyde **130** was elaborated *via* a Stork-Zhao olefination to furnish the full carbon skeleton and also the *seco* precursor for the ring-closing intramolecular Stille reaction. To our delight, the critical macrocyclisation delivered the protected natural product with complete retention of olefin geometry. A final global deprotection concluded our total synthesis of chivosazole F (4) in 20 steps and 2.5% overall yield. Our success in this arduous campaign hinged upon

careful initial analysis and planning, which fortunately, allowed for a highly convergent approach and a succinct endgame sequence. While we recognised the potential lability of such advanced polyene fragments, we could not have anticipated the frustration it brought. In this case, it truly stressed the importance of a flexible, modular strategy and the ability to adapt the strategy as required.



Scheme 23. Revised fragment coupling and completion of the total synthesis of chivosazole F (4)

Conclusions

555 Our recent synthetic endeavours towards these highly challenging classes of complex polyketides not only showcases the versatility of our group's aldol methodology, but also highlights the trials and tribulations we overcame in a sustained campaign to achieve these enticing targets. In our total synthesis of spirastrellolide A methyl ester, we discovered that the subtle, unexpected structural effects imposed by distal protecting groups proved to be highly
560 consequential in the critical macrolactonisation. Similarly, for rhizopodin, a carefully choreographed sequence of protecting group incorporation and selective deprotection, was pivotal to achieving the target. Our campaign towards leiodermatolide underlines the need to reassess fragment coupling strategies when required. This is a common theme and important lesson – and was certainly a defining obstacle in our campaign towards chivosazole F. In the
565 end, a carefully orchestrated sequence of fragment coupling steps proved to be vital for success.

In this account, the highlighted setbacks and accompanying explanations of strategy evolution serve to illuminate the unanticipated difficulties that can make or break a total synthesis. Overall, we are provided with a humbling reminder that despite continual advances in the field of chemical synthesis, there is still much to be learned from tackling a structurally
570 complex natural product.

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890 **Table of Contents**

Recent advances in the development of aldol-based synthetic routes to bioactive
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